

REMARKS

Claims 1-5 and 11-14 are pending and under examination. Applicants have canceled claims 6-10 without prejudice or disclaimer of the subject matter of those claims. Applicants have also amended claims 1, 11, 12, and 14. The specification supports these amendments at, for example, page 3, lines 33-37; page 5, lines 15-22; and page 7, lines 20-26. Thus, these amendments do not add new matter.

Applicants acknowledge with appreciation the Office's withdrawal of the prior rejection under 35 U.S.C. § 112, second paragraph, and the prior rejections under 35 U.S.C. § 102. The Office maintains the prior rejection under 35 U.S.C. § 103 and introduces new grounds for rejection under 35 U.S.C. § 102 as allegedly necessitated by Applicants' claim amendments in the previously filed response or by a previously filed Information Disclosure Statement. Applicants address these rejections below.

Rejections Under 35 U.S.C. § 102

Claims 1, 2, 6, 7, and 11-14 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by WO 02/10349 ("Yamato") as evidenced by Shimizu et al., Biomaterials 24:2309-16 (2003) ("Shimizu"). Office Action, page 2. The Office relies on published US patent application US 2004/0028657 as an English equivalent to Yamato.

According to the Office, Yamato teaches a method for producing a multi-layered cultured skin sheet comprising (a) culturing epidermal cells on a cell culture support coated with a temperature-responsive polymer with a lower critical solution temperature of 0-80°C in water, (b) bringing the culture temperature below the lower critical solution temperature, (c) bringing the epidermal sheet into close contact with a polymer membrane, (d) peeling the adhering sheet off of the cell culture support together with

the polymer membrane, and (e) allowing the cultured cell sheet in close contact with the polymer membrane to adhere to a temperature-responsive polymer followed by peeling off the polymer membrane that was in close contact with the epidermal sheet to form multiple cell layers. See *id.* at 3. Yamato also allegedly teaches an alternate embodiment in which the cellular sheet in contact with the polymer membrane is turned over and fixed on a cell culture support so that the polymer membrane contacts the support, followed by addition of a second cellular sheet in which the polymer membrane for the second sheet is removed before addition of yet another cellular sheet. See *id.* The Office also contends that Yamato discloses several types of polymers that could be used as a polymer membrane. See *id.* at 3 and 4.

When describing the resulting cell sheets, Yamato allegedly explains that the cell-to-cell substrate protein resembling the basal lamina that was formed during the culture has not been destroyed enzymatically and remains intact. See *id.* at 4. The Office relies on Shimizu to allegedly show that the basal lamina underneath Yamato's cell sheet would constitute a "distinct permeable sheet." *Id.* Applicants address this rejection with respect to claims 1, 2, and 11-14, which are still pending.

Solely to advance prosecution and without acquiescing to this rejection, Applicants have amended claims 1, 11, and 14 to indicate that the cells are flat-cultured on a permeable sheet. *Arguendo*, even if one were to equate Yamato's polymer membrane or extracellular matrix (ECM) with a permeable sheet, which Applicants do not, Yamato does not teach culturing cells on the polymer membrane. Likewise, Shimizu does not teach flat-culturing cells on the ECM. Because Yamato does not teach each and every element of independent claims 1, 11, and 14, this reference

cannot anticipate claims 1, 2, and 11-14. Applicants request that the Office withdraw this rejection accordingly.

The Office now rejects claims 1-3, 6-8, and 11 under 35 U.S.C. § 102(b) as allegedly anticipated by Yamato et al., *Material Integration* 13:58-64 (2000) ("Yamato2"). Office Action, page 7. According to the Office, Yamato2 teaches a "three-dimensional co-culture comprising combining, layering, and overlaying cell sheets." *Id.* Yamato2 also allegedly teaches that "each cell sheet that has been recovered from temperature-responsive culture dishes contains an extracellular matrix (ECM) formed during the culture underneath the cell monolayer" *Id.* The Office argues that this ECM, which is formed as the cells are cultured, would constitute a permeable sheet. *See id.* Applicants address this rejection with respect to claims 1-3 and 11, which are still pending.

As noted above, Applicants have amended claims 1 and 11 to indicate that the cells are flat-cultured on a permeable sheet. The Office's own description of Yamato2 indicates that the ECM, which the Office equates to a permeable sheet, forms during the culturing of the cells. Thus, even if one were to agree that the Yamato2's ECM represented a permeable sheet, which Applicants do not, this ECM forms only during the culturing of the cells and does not exist prior to cell culturing. In contrast, independent claims 1 and 11 indicate that the cells are cultured on a permeable sheet. Because Yamato2 does not teach each and every element of independent claims 1 and 11, this reference cannot anticipate claims 1-3 and 11. Applicants therefore request that the Office withdraw this rejection.

Rejection Under 35 U.S.C. § 103

The Office continues to reject claims 1-10 under 35 U.S.C. § 103(a) as allegedly obvious over WO 02/088332 ("Mitaka") in view of U.S. Patent 7,521,231 ("Germain"). Office Action, page 8. Referring to published U.S. application 2004/00073391 as an alleged English equivalent of Mitaka, the Office contends that Mitaka discloses a method of "inducing liver tissue from small hepatocyte colonies by placing the hepatocyte-rich colonies onto a sheet of biocompatible material . . . and further culturing them for a given period of time." *Id.* at 9. The Office also alleges that Mitaka includes collagen sheets, collagen sponges, and polyglycolic acid sheets as biocompatible materials and demonstrates that bile canaliculi form when small hepatocytes were seeded on a collagen sheet or a polyglycolic acid sheet. *See id.*

Acknowledging that Mitaka does not teach constructing a three-dimensional tissue by stacking flat-cultured hepatocytes on a permeable sheet, the Office turns to Germain. According to the Office, Germain teaches a "method for preparing a human or animal tissue by applying a compressive force to a stack of sheets of living tissue thereby inducing adjacent layers to fuse or adhere to each other with each sheet of living cells is comprised of cells and an endogenous extracellular matrix." *Id.* at 6. Germain also allegedly suggests that "multi-layer tissue constructs are thicker and therefore stronger and . . . can be designed to more closely resemble the tissues that they intended to replace." *Id.* at 10.

Based on these alleged teachings in Mitaka and Germain, the Office concludes that it would have been obvious to "modify the teachings of Mitaka . . . by forming a multi-layer liver tissue construct by applying compressive force to a stack of sheets

made of biocompatible material . . . seeded with cultured small hepatocyte-rich colonies in light of . . . Germain.” *Id.* The skilled artisan would have been motivated to make this combination, the Office reasons, because of the properties of multi-layer tissue constructs allegedly taught by Germain. Applicants address this rejection with respect to claims 1-5, which are still pending.

To facilitate prosecution, Applicants have amended independent claim 1 to indicate that the claimed method *consists essentially of* two steps: (a) flat-culturing cells on a permeable sheet; and (b) constructing a three-dimensional tissue with the permeable sheet by stacking cells flat-cultured on the permeable sheet on other flat-cultured cells. As the Office notes, Mitaka does not teach constructing a three-dimensional tissue by stacking flat-cultured hepatocytes on a permeable sheet. Due to this omission in Mitaka, the Office turns to Germain for instruction on how to combine cellular sheets.

As previously argued by Applicants, Germain instructs that “it is *essential* to be able to fuse adjacent layers of cell tissue together so that the layers are bonded together as firmly and reliably as possible and resist separation. If these layers of tissue are not fused together well, they may separate or come apart over time. . . .” Col. 1, lines 52-56, emphasis added. In sum, Germain, the only reference in the combination of Mitaka and Germain that allegedly provides instruction on how to combine cell sheets, teaches that it is essential to perform the step of fusing layers of cells together. Applicants contend that such a fusing step would materially affect the basic and novel characteristics of the claimed method and therefore would not be included in the method of claim 1. Because Germain expressly teaches away from the claimed method

and Mitaka is silent on a procedure for combining cell sheets, the combination of these references would not have rendered independent claim 1 or dependent claims 2-5 obvious. Applicants request that the Office withdraw this rejection accordingly.

Conclusions

Applicants respectfully request that the Office enter this Amendment under 37 C.F.R. § 1.116, placing claims 1-5 and 11-14 in condition for allowance. Applicants submit that the proposed amendments of claims 1, 11, 12, and 14 do not raise new issues or necessitate the undertaking of any additional search of the art by the Office, since all of the elements and their relationships claimed were either earlier claimed or inherent in the claims as examined. Therefore, this Amendment should allow for immediate action by the Office.

Furthermore, Applicants respectfully point out that the final action by the Office presented some new arguments as to the application of the art against Applicants' invention. It is respectfully submitted that the entering of the Amendment would allow Applicants to reply to the final rejections and place the application in condition for allowance.

Finally, Applicants submit that the entry of the Amendment would place the application in better form for appeal, should the Office dispute the patentability of claims 1-5 and 11-14.

In view of the foregoing remarks, this claimed invention is neither anticipated nor rendered obvious in view of the prior art references cited against this application. Applicants therefore request the entry of this Amendment, the Office's reconsideration and reexamination of the application, and the timely allowance of claims 1-5 and 11-14.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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